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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/427,873	10/27/99	BOYD	M 175912

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EXAMINER	
PARKIN, J	
ART UNIT	**PAPER NUMBER**
1648	9

DATE MAILED: 05/04/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/427,873	Boyd, M. R.
Examiner	**Art Unit**
Jeffrey S. Parkin, Ph.D.	1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *5 Feb 2001*

2a) This action is **FINAL**. 2b) [X] This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *20-27* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) X Claim(s) *20-27* is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are objected to by the Examiner.

11) The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) All b) Some* c)☐ None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) X Notice of References Cited (PTO-892)
16) Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Detailed Office Action

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the response submitted 05 February, 2001. No amendments to the claims or new claims accompanied the submission. Claims 20-27 are currently under consideration.

35 U.S.C. § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 20-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed toward therapeutic or prophylactic methods for inhibiting viral infection in a host through the administration of an antiviral peptide comprising at least nine contiguous amino acids of SEQ ID NO.: 2, which has been designated cyanovirin-N or CV-N. CV-N is a single 101 amino acid protein containing two intrachain disulphide bonds. The protein fails to display any significant sequence homology to other known proteins. It appears that CV-N binds directly to HIV-1 gp120. Other limitations specify that a viral envelope glycoprotein may also be administered with the antiviral peptide of interest. Applicant further indicates (see p. 4, specification) that "yet another object of the present invention is

to provide a method of treating an animal, in particular a human, infected by a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-2 [sic-HIV-1] or HIV-2. A related object of the present invention is to provide a method of treating an animal, in particular a human, to prevent infection by a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-1 or HIV-2."

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating the antiviral activity of SEQ ID NO.: 2. The sequence of interest is 101 amino acids in length. It is not readily manifest which portion(s) of the molecule is responsible for the antiviral activity of the protein. The disclosure fails to identify those portions, and the specific amino acids contained therein, of CV-N that are required for antiviral activity.

2) The disclosure fails to teach which polypeptide fragments of "at least nine contiguous amino acids" contain the requisite determinants that are required for antiviral activity. For instance, should the amino terminal 10 amino acids be utilized?

What about the amino terminal 20, 30, or 40 amino acids? Should the carboxy terminal 10, 20, 30, or 40 amino acids be employed? Which peptide fragments can reasonably be expected to contain the determinants modulating the antiviral activity of the protein? Absent further guidance on the subject, the skilled artisan cannot make a reasonable determination as to which consecutive amino acids should be included in any given polypeptide.

3) The disclosure fails to provide any guidance pertaining to the binding specificity of CV-N, or polypeptide fragments thereof. It appears that CV-N binds to HIV-1 gp120 and inhibits efficient virion-cell binding and entry. However, the disclosure fails to provide any guidance pertaining to the molecular determinants modulating the binding interactions between CV-N and gp120. Moreover, since HIV-1 and HIV-2 display considerable genotypic/phenotypic heterogeneity in the *env* coding region, it is not readily manifest that CV-N would recognize the HIV-2 envelope. Moreover, it seems extremely unlikely, given the genetic unrelatedness of other enveloped viruses, that CV-N would be capable of binding to any other viruses.

4) The disclosure fails to provide any guidance pertaining to the ability of CV-N to inactivate natural HIV-1, or other viral isolates, as opposed to laboratory-adapted isolates. The lentiviruses, and many other viruses as well, exist as a quasispecies that includes viruses of differing genotypic and phenotypic properties. Many antiviral compounds are active against laboratory isolates, but fail to display the same activity when directed against viruses that are not laboratory-adapted.

5) The disclosure fails to provide any guidance pertaining to the immunologic properties of CV-N in its intended host. The administration of a foreign antigen such as CV-N will probably lead to the development of anti-CV-N antibody responses in the host of interest. These responses have the potential to become pathogenic.

6) The prior art teaches that the development of HIV-1 antivirals

has been a largely unsuccessful endeavor (Saunders, 1992; Wilting and Janknegt, 1991; Richman, 1996; Rice and Bader, 1995; Ramachandran *et al.*, 1994; Peto, 1992; Whittle and Blundell, 1994; Lee, 1997; and Allan, 1997) due to a number of factors such as the lack of suitable animal models and the quasispecies nature of HIV. For instance, Saunders (1992) reported that the results of recent clinical trials indicates that many non-nucleoside inhibitors of HIV reverse transcriptase are not efficacious, despite the positive results obtained from preliminary studies. The authors stated that "The intervening period has given rise to several such agents but recent clinical trial data has indicated this optimism to be premature." Wilting and Janknegt (1991) also reported that a number of problems have been associated with the development of effective antivirals. The authors noted that "There are only a limited number of effective, non-toxic antiviral drugs for clinical use, whereas there is a great need for such drugs. Especially for the treatment of patients infected with the human immuno-deficiency virus (HIV) anti-HIV drugs are required ... An increasing problem is the development of virus strains resistant to the available drugs."

A number of problems have also beleaguered those scientists that are specifically trying to develop peptide-based antivirals that block early viral lifecycle events similar to those of the instant invention. For instance, Rice and Bader (1995) addressed this topic and concluded that "Clinicians most likely will be hesitant to treat patients with compounds shown to act on virus-cell surface interactions, given the failure in the past of several such compounds in clinical studies." Ramachandran *et al.* (1994) also evaluated the clinical efficacy of a protein based conjugate (CD4-PE40) that inhibits the early stages of viral entry. The authors concluded that the results obtained from a phase III clinical trial were not promising and the authors concluded that "The relative

resistance of clinical isolates of HIV, limits of the tolerated dose, and the immunogenicity and short half-life of the protein may explain the lack of *in vivo* antiviral effect of CD4-PE40."

7) The claims are of excessive breadth and are not adequately supported by the disclosure. The claims broadly encompass methods of treating any viral infection and could include DNA viruses, RNA viruses, or retroviruses of vastly different genotypic compositions and phenotypic activities. Moreover, the claims broadly encompass methods that may employ various CV-N polypeptide fragments. However, as noted *supra*, the disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating the antiviral and binding activities of the cyanovirin. Absent such guidance, the skilled artisan has only been extended an undue invitation to further experimentation.

8) The disclosure fails to provide a sufficient number of working embodiments that would enable the full breadth of the claimed invention. Perusal of the specification resulted in the identification of an *in vitro* screening assay involving CEM cells and the isolate HIV-1_{RF}. However, it has been well-documented that simple *in vitro* screening assays are not predictive of clinical efficacy (Saunders, 1992; Wiltink and Janknegt, 1991; Richman, 1996; Rice and Bader, 1995; Ramachandran *et al.*, 1994; Peto, 1992; Whittle and Blundell, 1994; Lee, 1997; and Allan, 1997). As Whittle and Blundell (1994) note, the rational design of antivirals is a difficult process. Random *in vitro* drug screening assays are only a rudimentary first step in the identification of efficacious antiviral agents. As the authors conclude, "while it [structure-based drug design] can be of great use in the initial process of identifying ligands with improved affinity and selectivity *in vitro*, it can usually say very little about other essential aspects of the drug discovery process, e.g., the need to achieve an adequate pharmacokinetic profile and low toxicity *in vivo*."

Accordingly, the results obtained from this assay do not constitute an appropriate working embodiment.

Applicant also provided a Declaration under 37 C.F.R. § 1.132 involving data obtained from an SIV model. A gel comprising CV-N was applied intrarectally or intravaginally and an inoculant comprising the virus SHIV89.6P administered. Appropriately drafted claim language directed toward this embodiment would be acceptable. However, the SIV/SHIV model is not an accurate predictor of clinical efficacy (Lee, 1997; Allan, 1997; Rice and Bader, 1995). Lee (1997) reports that "there is no convincing basis to conclude that protection observed in any of the animal models is suitable to predict vaccine efficacy in humans." Allan also emphasizes some of the limitations associated with the SIV/SHIV model. The author reported that "One disadvantage to this model is that there is currently no disease association." Rice and Bader (1995) also add that "the final test of a drug's efficacy comes in the clinical experience."

The declaration also failed to address a number of other important issues. For instance, the declaration was silent pertaining to challenge studies involving different HIV-1 and -2 isolates, as well as, other viral isolates (i.e., FIV, BIV, EIAV, CAEV, HSV, CMV, HTLV, etc.). Insufficient guidance was provided concerning the ability of CV-N to inactivate physiologically relevant concentrations of HIV-1, HIV-2, or other viruses. The declaration was also silent pertaining to the pharmacological and therapeutic profile of CV-N. The experimental model employed failed to measure reductions in viral load. It has been well-documented that HIV-1-infected patients produce upwards of 1×10^{10} virions per day. It seems unlikely that adequate concentrations of the CV-N protein can be maintained over sufficient periods of time to provide any meaningful effect. The experimental model employed did not provide any guidance pertaining to the pharmacological properties of the peptide. Many compounds fail to display clinical

efficacy because of pharmacological concerns (i.e., binding and inactivation by serum proteins, rapid clearance rate, poor circulating half-life, inability to target the tissue of interest [i.e., the lymphatic compartment]). However, none of these properties were addressed in the declaration. Thus, the skilled artisan cannot make an meaningful deductions pertaining to the therapeutic properties of the antiviral composition.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Obviousness-Type Double Patenting

4. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel,* 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum,* 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi,* 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman,* 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993).

5. A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

6. Claims 20 and 21 are **provisionally** rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-24 of copending Application Serial No. 09/428,275. Although the conflicting claims are not identical, they are not patentably distinct from each other. Both sets of claims are directed toward methods of inhibiting viral infections through the administration of a cyanovirin containing SEQ ID NO.: 2. The two sets of claims do not include any novel or distinguishing features. Thus, for all intensive purposes, the claims appear to be directed toward the same invention. This is a **provisional** obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Claims 20 and 21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-19 of U.S. Patent No. 6,015,876. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the '876 patent are directed toward methods of contacting a virus with a cyanovirin containing SEQ ID NO.: 2. The claims of the instant application are directed toward methods of treating viral infections through the administration of a cyanovirin containing SEQ ID NO.: 2. Although it is not specifically recited in the claims, such inhibitory methods would inherently involve a contact step between the antiviral agent and virus. Accordingly, the claims are not patentably distinct from each other.

Correspondence

8. The Art Unit location of your application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1648.**

9. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

10. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

23 April, 2001

JSP:cf(#337675)